(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10798 A1

(51) International Patent Classification[7]: C07B 61/00, C07D 263/34, 263/32, 277/56, 277/20, 413/12, 417/12, C07K 5/078

(21) International Application Number: PCT/US00/21051

(22) International Filing Date: 2 August 2000 (02.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/147,451 4 August 1999 (04.08.1999) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

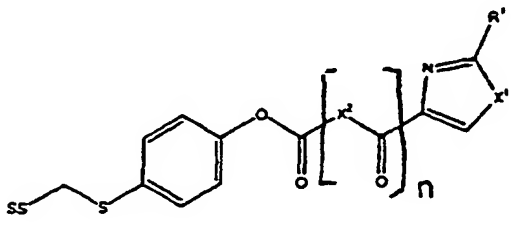
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/10798 A1

(54) Title: SOLID PHASE SYNTHESIS OF OXA- AND THIAZOLES



(α)

(57) Abstract: Thia- and oxazole-4-carboxylic acid derivatives are prepared by solid phase synthesis, using intermediates of formula (α) where SS is a solid support and n is 0 or 1.

SOLID PHASE SYNTHESIS OF OXA-AND THIAZOLES

FIELD OF INVENTION

The present invention relates to solid phase and combinatorial synthesis of oxazole and thiazole derivatives.

BACKGROUND OF THE INVENTION

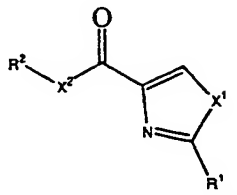
Organic compounds of potential therapeutic interest are traditionally synthesized and evaluated one at a time, thus dramatically limiting the number of derivatives that can be synthesized and screened against a specific receptor or enzyme. It is therefore desirable to develop new synthetic methodology for synthesizing a large number (library) of compounds of potential therapeutic interest, such as small heterocyclic compounds. Oxazoles and thiazoles are a class of heterocyclic compounds having potential use as pharmaceuticals. There is thus a continuing need for processes that facilitate the synthesis of a large number of compounds in a relatively short period of time.

The realization of known synthetic reactions on a solid support may not always be possible and may require careful optimization of the reaction conditions. For example, liquid phase reaction conditions may not be amenable with some types of supports or liquid phase reactions may require precise temperature adjustment in arrays of reactors for solid phase synthesis. Additionally, the classical tools for the quality control of intermediates (infrared spectroscopy, nuclear magnetic resonance spectroscopy and mass spectroscopy) may only be of limited use in solid phase synthesis.

For these reasons, the implementation of known liquid phase reactions to a solid support may often require a major effort and time investment. However, solid phase synthesis, once implemented and optimized, offers many advantages if compared to synthesis in liquid phase. The advantages of the present invention are the production of a large number of diverse oxazole and thiazole compounds, synthesized by a time and cost efficient process. Further advantages of the present invention will become apparent from a consideration of the ensuing description.

SUMMARY OF THE INVENTION

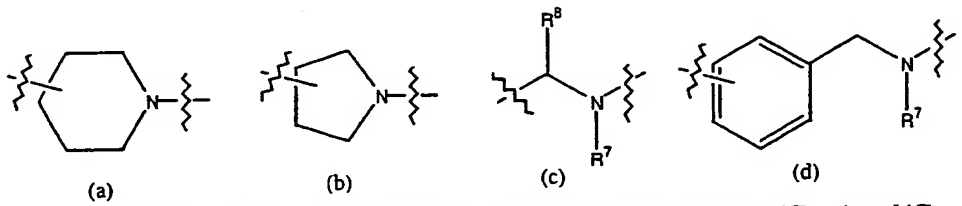
Keeping the above-discussed needs in mind, the present invention provides a



process for the synthesis of a compound or an array of compounds represented by Formula I in which:

X^1 is O or S;

R^1 is $-R^3$, $-NR^3R^4$, $-NR^3C(NR^4)NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is



(a) (b) (c) (d)

(C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, polycyclo(C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^3NR^5R^5$, $-X^3NR^5C(O)R^5$, $-X^3NR^5C(O)OR^5$, $-X^3NR^5C(O)NR^5R^5$ and $-X^3NR^5C(NR^5)NR^5R^5$, wherein X^3 is a bond or methylene and R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl; X^2 is a group selected from Formulae (a), (b), (c) and (d):

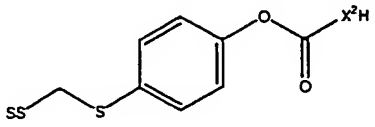
R^2 is $-CH_2OH$, $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, wherein R^9, R^{10} and R^{11} independently are hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl or $-X^4R^{12}$, wherein X^4 is (C_{1-4})alkylene and R^{12} is $-OR^{13}$ or $-NR^{13}R^{14}$, wherein R^{13} and R^{14} are independently hydrogen, (C_{1-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl,

heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl, $-X^4OR^{16}$ or $-X^4NR^{16}R^{16}$, wherein X^4 is as defined above and R^{16} at each occurrence independently is hydrogen or (C_{1-2})alkyl, wherein any aromatic moieties comprising R^9, R^{10} or R^{11} optionally independently are substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^4NR^5R^5$, $-X^4NR^5C(O)R^5$, $-X^4NR^5C(O)OR^5$, $-X^4NR^5C(O)NR^5R^5$ and $-X^4NR^5C(NR^5)NR^5R^5$, wherein X^4 and R^5 are as defined above, or R^9 and R^{10} together with the nitrogen atom to which R^9 and R^{10} are attached form hetero(C_{5-7})cycloalkyl optionally substituted with $-X^4R^{12}$, wherein X^4 and R^{12} are as defined above;

R^7 is hydrogen or (C_{1-4})alkyl; and

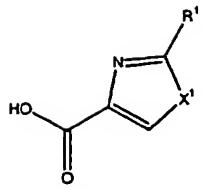
R^8 is (i) hydrogen, (ii) (C_{1-6})alkyl optionally substituted with $-OR^{17}$, $-SR^{17}$, $-S(O)R^{17}$, $-S(O)_2R^{17}$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{18}$, $-NR^{17}R^{18}$, $-NR^{18}C(O)R^{17}$, $-NR^{18}C(O)OR^{17}$, $-NR^{18}C(O)NR^{17}R^{18}$ or $-NR^{18}C(NR^{18})NR^{17}R^{18}$, wherein R^{17} is (C_{1-6})alkyl, (C_{1-6})alkanoylaminomethyl, (C_{3-12})cycloalkyl(C_{0-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-3})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, (C_{6-12})arylsulfonyl, hetero(C_{5-12})aryl(C_{0-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-3})alkyl and R^{18} at each occurrence independently is hydrogen or (C_{1-6})alkyl, or (iii) (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{1-3})alkyl, hetero(C_{5-12})aryl(C_{1-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{1-3})alkyl; said process comprising:

(i) treating a compound of Formula A:



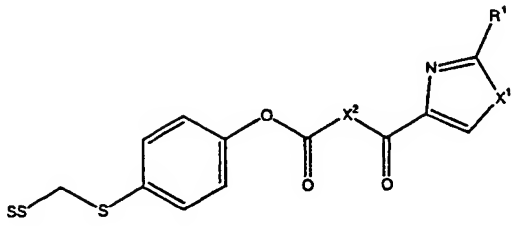
Formula A

with a compound of Formula B:



Formula B

in the presence of a coupling agent and optionally an acylation catalyst, to yield a compound of Formula C:

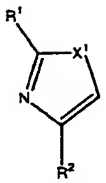


Formula C

where R^1, X^1 and X^2 are as defined above and "SS" represents a solid support; and

(ii) treating a compound or an array of compounds of Formula C with (a) a reducing agent to yield a compound or an array of compounds of Formula I where R^2 is CH_2OH, or (b) a compound of formula $R^9R^{10}NH$ or $R^{11}OH$ to yield a compound or an array of compounds of Formula I where R^2 is $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, respectively.

Another aspect of the preferred invention provides a process for synthesizing a compound or an array of compounds of Formula II,



Formula II

in which:

X^1 is O or S;

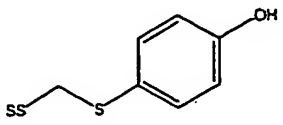
R^1 is $-R^3$, $-NR^3R^4$, $-NR^3C(NR^4)NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is (C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, polycyclo(C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^3NR^5R^5$, $-X^3NR^5C(O)R^5$, $-X^3NR^5C(O)OR^5$, $-X^3NR^5C(O)NR^5R^5$ and $-X^3NR^5C(NR^5)NR^5R^5$, wherein X^3 is a bond or methylene and R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl;

R^2 is $-CH_2OH$, $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, wherein R^9, R^{10} and R^{11} independently are hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl or $-X^4R^{12}$, wherein X^4 is (C_{1-4})alkylene and R^{12} is $-OR^{13}$ or $-NR^{13}R^{14}$, wherein R^{13} and R^{14} are independently hydrogen, (C_{1-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl, $-X^4OR^{16}$ or $-X^4NR^{16}R^{16}$, wherein X^4 is (C_{1-4})alkylene and R^{16} at each occurrence independently is hydrogen or (C_{1-2})alkyl, wherein any aromatic moieties comprising R^9, R^{10} or R^{11} optionally independently are substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^4NR^5R^5$, $-X^4NR^5C(O)R^5$, $-X^4NR^5C(O)OR^5$, $-X^4NR^5C(O)NR^5R^5$ and $-X^4NR^5C(NR^5)NR^5R^5$, wherein X^4 and R^5 are as defined above, or R^9 and R^{10} together

with the nitrogen atom to which R^9 and R^{10} are attached form hetero(C_{5-7})cycloalkyl optionally substituted with $-X^4R^{12}$, wherein X^4 and R^{12} are as defined above;

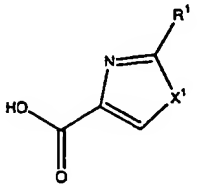
said process comprising:

(1) treating a compound of Formula D:



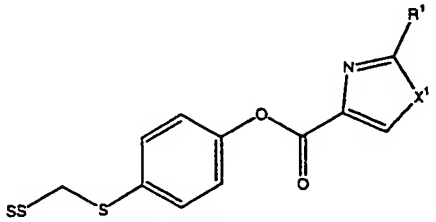
Formula D

with a compound of Formula B:



Formula B

in the presence of a coupling agent and optionally an acylation catalyst, to yield a compound of Formula E:



Formula E

where R^1 and X^1 are as defined above and "SS" represents a solid support; and

(2) treating a compound or an array of compounds of Formula E with (a) a reducing agent to yield a compound or an array of compounds of Formula II, where R^2

is CH_2OH, or (b) a compound of formula $R^9R^{10}NH$ or $R^{11}OH$ to yield a compound or an array of compounds of Formula II where R^2 is $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, respectively.

DETAILED DESCRIPTION OF THE INVENTION

While the broadest definition of this invention is set forth in the Summary of the Invention, certain aspects of the invention are preferred.

For example, preferred is a process wherein step (i) comprises treating a compound of Formula A with a compound of Formula B in the presence of a coupling agent selected from DIC, PyBOP or HATU and an acylation catalyst selected from DMAP or 4-pyrrolidinopyridine.

A preferred embodiment is a process wherein step (1) comprises treating a compound of Formula D with a compound of Formula B in the presence of a coupling agent selected from DIC, PyBOP or HATU and an acylation catalyst selected from DMAP or 4-pyrrolidinopyridine.

A further preferred process of the present invention is one wherein steps (i) and (1) are carried out in the presence of an inert solvent selected from DCM, THF and chloroform and at a temperature ranging from about 15°C to about 35°C.

Preferred is a process wherein the inert solvent in steps (ii) and (2) are selected from THF, methylene chloride, DCM, ethyl acetate, DMF, dioxane, chloroform and DMSO; and the reactions are carried out at a temperature ranging from about -30°C to about 35°C.

A further preferred embodiment of the present invention is where the reducing agent in steps (ii)(a) and (2)(a) is $LiBH_4$.

Preferred is a process wherein steps (ii)(b) and (2)(b) are carried out at a temperature ranging from about 10°C to about 50°C.

Another aspect of the present invention provides an array of compounds synthesized by the processes of the present invention.

Yet another aspect of the present invention provides a process for synthesizing a compound or an array of compounds of Formula C.

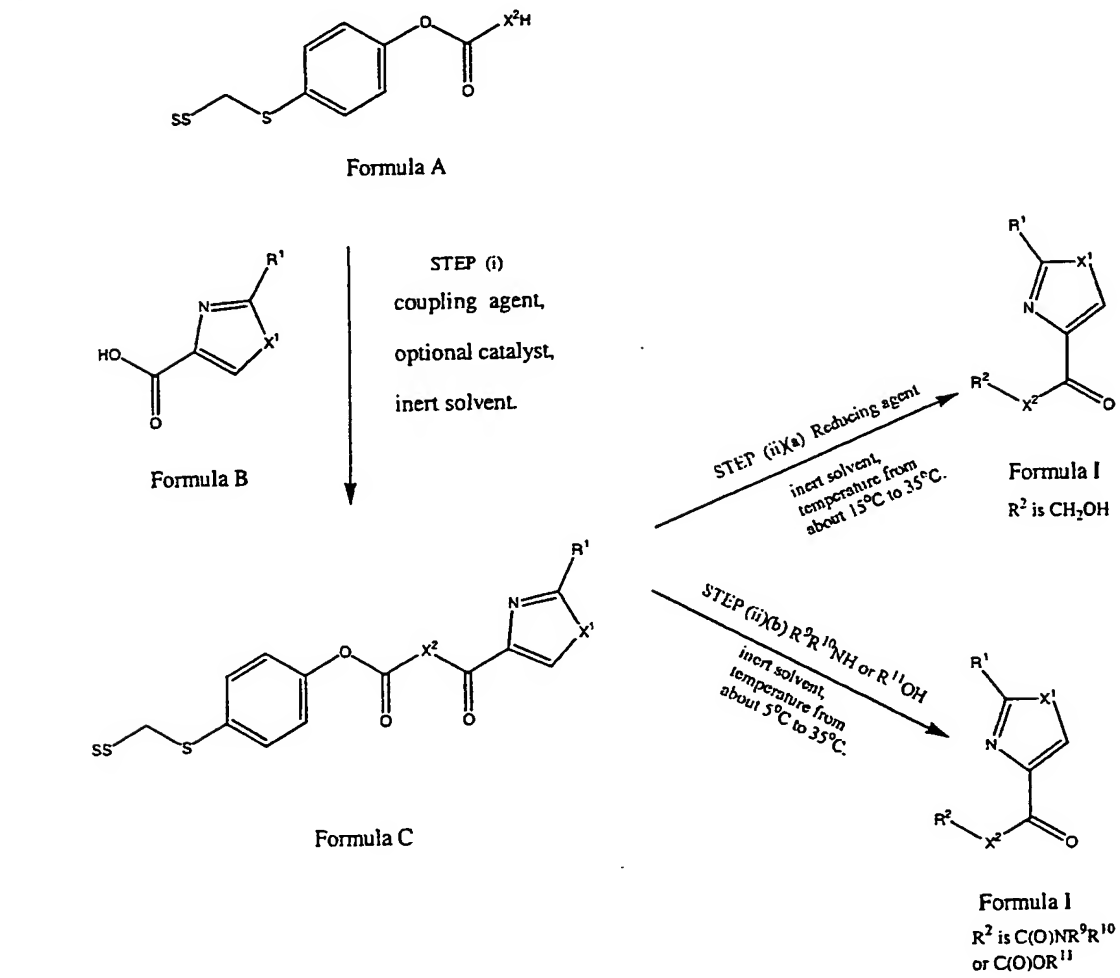
Preferred is a process for synthesizing a compound or an array of compounds

of Formula E.

EXPERIMENTAL DETAILS

The novel process of the present invention to synthesize compounds of Formula I is described in Scheme A, below:

Scheme A



General Synthetic procedure

The novel process outlined in Scheme A above can be used to synthesize compounds of Formula I wherein X^1, X^2, R^1 R^2, R^9, R^{10} and R^{11} are as described in the Summary of the Invention. The general description of each step of this process is discussed below.

Synthesis of Compounds of Formula C (Step (i))

A compound of Formula B (1 equivalent) and a coupling agent, preferably DIC (1 equivalent), are dissolved in an inert solvent (e.g., DCM; 15 mL/g of Formula B). The resulting solution is allowed to stand for 5 to 15 minutes. The compound of Formula A (1-10 equivalents) is swelled in a suitable inert solvent (e.g., DCM at 10mL/g of Formula A) and added to the mixture of Formula B, DIC and DCM. An acylation catalyst (e.g., DMAP; 0.4-1.2 equivalents), may be added to the reaction mixture. The mixture is agitated, with frequent venting, at a temperature between about 10°C and about 40°C for about 10 to about 24 hours. The resin is isolated from solvents and washed free of contaminants and dried to yield purified compound of Formula C. For example, the resin is typically washed in succession with: 1:1 DCM:THF (x1); DCM (x2); MeOH (x2); and dioxane (x3); and dried under reduced pressure.

Synthesis of Compounds of Formula I (Step (ii)(a))

Compounds of Formula I, where R^2 is CH_2OH, are prepared by treating compounds of Formula C with a reducing agent (alkaline borohydrides e.g., $NaBH_4$ or $LiBH_4$). The reaction typically is carried out by mixing an inert solvent suspension of the compound of Formula C with a reducing agent, preferably $LiBH_4$, in a suitable solvent (e.g., THF). This mixture is agitated for about 10 to about 24 hours at a temperature of from about -30°C to about 35°C. This reaction mixture is filtered and the filter is washed through with a suitable solvent (e.g., dioxane). The combined filtrate is lyophilized to yield compounds of Formula I in relatively pure form. Compounds of Formula I can be purified further, as necessary, using the solid supported liquid-liquid extraction (SLE) procedure of Johnson et al. as described in

Tetrahedron 54 (1998) 4097-4106.

Synthesis of Compounds of Formula I (Step (ii)(b))

Compounds of Formula I, where R^2 is $C(O)NR^9R^{10}$, are prepared by treating a suspension of a compound of Formula C with a solution of an amine of formula $R^9R^{10}NH$. Typically, the reaction is carried out in an inert solvent (e.g., dioxane, DCM, THF, preferably dioxane). The resulting mixture is gently agitated for about 10 to about 24 hours at temperatures between about 10°C and about 40°C. The reaction mixture then is filtered and the filter washed through with dioxane. The combined filtrate is collected and lyophilized to obtain compounds of Formula I in relatively pure form. Compounds of Formula I can be purified further by performing a solid supported liquid-liquid extraction (SLE) as described by Johnson et al. in Tetrahedron 54 (1998) 4097-4106.

Compounds of Formula I, where R^2 is $C(O)OR^{11}$, are prepared by treating a suspension of a compound of Formula C with a compound of Formula $R^{11}OH$. The reaction mixture is gently agitated for about 10 to about 24 hours at temperatures between about 30°C and about 50°C. The reaction mixture then is filtered and the filter washed through with a suitable solvent (e.g., dioxane, DCM, THF, preferable dioxane). Typically, the reaction is carried out in the presence of a non-nucleophilic base (e.g., triethylamine (TEA), trimethylamine or pyridine, preferably TEA) and in a suitable inert solvent (e.g., dioxane, DCM, THF, preferably dioxane). The combined filtrate is lyophilized to yield compounds of Formula I.

Starting Materials

Compounds of Formula A and Formula B can be prepared by synthetic methods known to one skilled in the art. Illustrative methods to prepare compounds of Formula A and Formula B are discussed below.

Preparation of a compound of Formula A

A solution of sodium methoxide in a suitable solvent, preferably DMF, is cooled to about 0°C and then heated with 4-hydroxythiophenol (typically 1

equivalent). This mixture is agitated for up to 2 hours at ambient temperature and then combined with a suitable solid support, e.g., Merrifield resin (Midwest Biotech), in DMF. The resulting mixture is agitated for up to 60 hours at a temperature of about 60°C. The resin is isolated from solvents and washed free from contaminants with suitable inert solvents. For example, resin is washed up to three times in succession with DMF, MeOH, AcOH, 1N HCl:AcOH (5% v:v), DCM, MeOH and Et_2O to yield a thiophenol resin.

A carboxylic acid comprising a protected amino group (1 equivalent), solvated in an inert solvent (e.g., dioxane, DCM, THF, preferably DCM), is mixed with a coupling agent, preferably DIC (typically 1 equivalent), and allowed to stand for 5 to 15 minutes. The resultant complex is added to the thiophenol resin from above and an acylation catalyst (e.g., DMAP; 0.1 equivalents) and the resulting mixture is agitated for 10 to 24 hours at ambient temperatures. The resin is isolated from solvents, washed free of contaminants and dried to yield a resin protected compound of Formula A. For example, the resin is typically washed in succession with 1:1 DCM:THF (x1), DCM (x3) and MeOH (x3). The protective group is then removed by, for example, hydrolysis of the resin with a suitable acid (preferably TFA; 10mL/g of resin) in the presence of an inert solvent (preferably DCM) for about one hour. The resin is isolated from solvents and washed free of contaminants to yield compounds of Formula A. For example, the resin is typically washed in succession with DCM (x2), 15% (v:v) TEA in DCM (x2), MeOH (x2) and DCM (x2).

Carboxylic acids comprising a Boc protected amino group, e.g. Boc-nipecotic acid or Boc-4-aminomethylbenzoic, may be obtained commercially (e.g., Novabiochem) or may be synthesized by the process described in Bodanszky and Bodanszky, *The Practice of peptide Synthesis*: Springer-Verlag: New York, 1984.

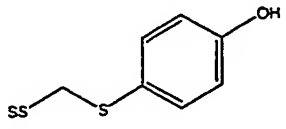
Preparation of a compound of Formula B

Compounds of Formula B (wherein X^1 is sulfur) may be prepared by Hantsch condensations of ethylbromopyruvate with thioureas and thioamides. A detailed procedure is described by Chucholowski et al., (*Chimia*, 50, 1996, 525-530) and Hantsch, A., (*Ber.* 1890, 23, 1474).

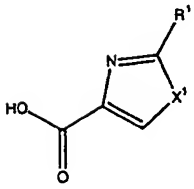
Compounds of Formula B (wherein X^1 is oxygen) may be prepared from serine or threonine methyl esters as described by Wipf and Miller (*Tetrahedron Letters*, Vol. 33, No. 7, pp. 907-910, 1992) and Williams et al. (*Tetrahedron Letters*, Vol. 38, pp. 331-334, 1997).

Another aspect of the present invention provides a process for synthesizing compounds of Formula II. The novel process is described in Scheme B, below:

Scheme B

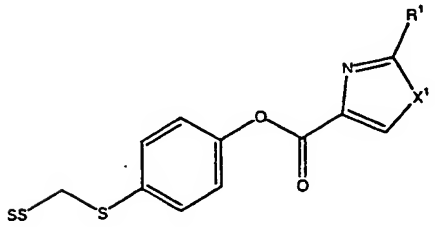


Formula D



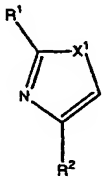
Formula B

STEP (1)
coupling agent,
optional catalyst,
inert solvent



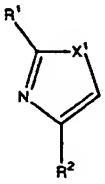
Formula E

STEP (2)(a) Reducing agent
inert solvent,
temperature from
15°C to 35°C



Formula II
R^2 is $CH_2(OH)$

STEP (2)(b) $R^9R^{10}NH$ or $R^{11}OH$
inert solvent,
temperature from
5°C to 35°C



Formula II
R^2 is $C(O)NR^9R^{10}$
or $C(O)OR^{11}$

General Synthetic procedure

The novel process outlined in Scheme B above can be used to synthesize compounds of Formula II wherein X^1, R^1 R^2, R^9, R^{10} and R^{11} are as described in the Summary of the Invention. The general description of each step of this process is as given below.

Synthesis of Compounds of Formula E (Step (1))

A compound of Formula B (1 equivalent) and a coupling agent, preferably DIC (1 equivalent), are dissolved in an inert solvent (e.g., DCM; 15 mL/g of Formula B). The resulting solution is allowed to stand for 5 to 15 minutes. The compound of Formula D (1-10 equivalents) is swelled in a suitable inert solvent (e.g., DCM at 10mL/g of Formula D) and added to the mixture of Formula B, DIC and DCM. An acylation catalyst (e.g., DMAP; 0.4-1.2 equivalents) may be added to the reaction mixture. The mixture is agitated, with frequent venting, at a temperature between about 10°C and about 40°C for about 10 to 24 hours. The resin is isolated from solvents, washed free of contaminants and dried to yield a compound of Formula E. For example, the resin is typically washed in succession with 1:1 DCM:THF (x1), DCM (x2), MeOH (x2) and dioxane (x3).

Synthesis of Compounds of Formula II (Step (2)(a))

Compounds of Formula II, where R^2 is CH_2OH, are prepared by treating compounds of Formula E with a reducing agent (alkaline borohydrides e.g., $NaBH_4$ or $LiBH_4$. The reaction is typically carried out by mixing an inert solvent suspension of the compound of Formula E with a reducing agent, preferably $LiBH_4$, in a suitable solvent (e.g., THF). This resulting mixture is agitated for about 10 to about 24 hours at a temperature of from about 5°C to about 35°C. This reaction mixture is filtered and the filter is washed through with a suitable solvent (e.g., dioxane). The combined filtrate is lyophilized to yield compounds of Formula II in relatively pure form. Compounds of Formula II can be purified further, as necessary, using the solid supported liquid-liquid extraction (SLE) procedure of Johnson et al. as described in Tetrahedron 54 (1998) 4097-4106.

Synthesis of Compounds of Formula II (Step (2)(b))

Compounds of Formula II, where R^2 is $C(O)NR^9R^{10}$, are prepared by treating a suspension of a compound of Formula E with a solution of an amine of formula $R^9R^{10}NH$. Typically the reaction is carried out in an inert solvent (e.g., dioxane, DCM, THF, preferably dioxane). The resulting mixture is agitated for 10 to 24 hours at temperatures between about 10°C and about 40°C. The reaction mixture then is filtered and the filter washed through with dioxane. The combined filtrate is lyophilized to obtain compounds of Formula II in relatively pure form. Compounds of Formula II can be purified further by performing a solid supported liquid-liquid extraction (SLE) described by Johnson et al., in *Tetrahedron* 54 (1998) 4097-4106.

Compounds of Formula II, where R^2 is $C(O)OR^{11}$, are prepared by treating a suspension of a compound of Formula E with a compound of formula $R^{11}OH$. Typically the reaction is carried out in the presence of a non-nucleophilic base (e.g., triethylamine (TEA), trimethylamine or pyridine, preferably TEA) and in a suitable inert solvent (e.g., dioxane, DCM, THF, preferably dioxane). The reaction mixture is agitated for 10 to 24 hours at temperatures between about 30°C and about 50°C. The reaction mixture is then filtered and the filter washed through with suitable solvents (e.g., dioxane). The combined filtrate is lyophilized to yield compounds of Formula II.

Preparation of Compounds of Formula D and Formula B

Compounds of Formula D and Formula B can be prepared by synthetic methods known to one skilled in the art. Compounds of Formula B are prepared as discussed for Scheme A, above. An illustrative method to prepare a compound of Formula D is discussed below.

Preparation of a compound of Formula D:

A solution of sodium methoxide (typically about 1.387 mol in a suitable solvent, preferable DMF) is cooled to about 0°C and then heated with 4-hydroxythiophenol (typically 1 equivalent). This mixture is agitated for up to 2 hours at ambient temperature and then combined with a suitable solid support, e.g.,

Merrifield resin (Midwest Biotech) in DMF. The resulting mixture is agitated for up to 60 hours at a temperature of about 60°C. The resin is isolated from solvents and washed free from contaminants with suitable inert solvents to yield a compound of Formula D. For example, typically the resin is washed up to three times in succession with DMF, MeOH, AcOH, 1N HCl:AcOH (5% v:v), DCM, MeOH and Et_2O.

Synthesis of an Array of Compounds of Formula I or Formula II

The novel process of the present invention can also be used to prepare an array of compounds of Formula I or Formula II. The following description is the general procedure to accomplish such a synthetic array.

The resin-supported compounds of Formula C or Formula E are suspended in dioxane (40ml) and partitioned into Polyfiltronics™ plates (2.7μm). The plates are placed in Hydra™ clamps and the Hydra™ is then used to dispense in to each well, either (i) 800 μL of 0.5M $R^9R^{10}NH$ in dioxane, (ii) 800 μL of dioxane:TEA:$R^{11}OH$ (8:1:1), or (iii) 800 μL of 2M $LiBH_4$ in THF diluted 1:3 in dioxane to each well. The wells are covered with a Teflon™ sheet and clamped. The $LiBH_4$ cleavage plates are shaken for 10 to 24 hours at temperatures between 5°C and 35°C. The amine ($R^9R^{10}NH$) cleavage plates are shaken for 10 to 24 hours at temperatures between 10°C and 40°C. The alcohol ($R^{11}OH$) cleavage plates are placed in the Hydra™ rotisserie oven on the rocker table apparatus for 10 to 24 hours at temperatures between 30°C and 50°C. The Formula I or Formula II products are collected by gravity filtration and minor N_2 positive pressure into 2mL Beckman™ plates. The resin in each well is then washed with 400 μL of dioxane and the filtrate is collected. The plates are frozen at –78°C and then lyophilized at 5°C for a 24 hour period on the Virtis™ tray lyophilizer. The cleaved residues are then taken up in 800 μL of DCM and shaken orbitally for 20 minutes. The compounds of Formula I or Formula II are then extracted through the SLE material (pre-primed with 2N HCl (350 μL) or H_20 (350 μL)) using the Tecan Genesis RSP 200 Series (Tecan, AG). The 2 mL Beckman™ product plates are then concentrated using the Savant™ Speedvac. All of the plates are then put in a large dessicator and vacuum dried for 10 to 24 hours.

Representative Compounds of Formula I

2-*p*-Tolyl-oxazole-4-carboxylic acid [1-butylcarbamoyl-2-phenyl-ethyl]-amide (Standard 1):

A compound of Formula A in which X^2 is a group of Formula (c) wherein R^7 is hydrogen and R^8 is benzyl and SS is Merrifield resin (3.2g) was swelled in DCM (32mL). This swelled compound was added to a mixture of 2-*p*-tolyl-oxazole-4-carboxylic acid (7.8g, 38.4mmol), DIC (6mL; 38.4mmol) and DCM (117 mL). The resulting solution was allowed to stand for 5 to 15 minutes. DMAP (140mg; 1.15mmol) was added and the resulting mixture was agitated, with frequent venting, at a temperature of about 25°C for about 15 hours. The resulting resin was isolated and washed in succession with 1:1 DCM:THF (1x100mL), DCM (2x100mL), MeOH (2x100mL) and dioxane (3x100mL) and dried under reduced pressure to yield the corresponding compound of Formula C in which X^1 is oxygen, R^1 is of 2-*p*-tolyl and X^2 is a group of Formula (c) wherein R^7 is hydrogen and R^8 is benzyl. The compound of Formula C was suspended in a minimal amount of dioxane and treated with 0.5M butylamine in dioxane (50 mL). The resulting mixture was agitated for 10 to 24 hours at a temperature of 25°C. The mixture was then filtered and the residue washed with dioxane (50 mL). The combined filtrate was collected and lyophilized to obtain 2-*p*-tolyl-oxazole-4-carboxylic acid (1-butylcarbamoyl-2-phenyl-ethyl)-amide (standard 1).

2-({2-[3-Benzyl-3-(2-methoxy-phenyl)-ureido]-thiazole-4-carbonyl}-amino) -3-benzylsulfanyl-propionic acid pent-2-ynyl ester (Standard 6):

2-[3-Benzyl-3-(2-methoxy-phenyl)-ureido]-thiazole-4-carboxylic acid (14.7g, 38.4mmol) and DIC (6mL; 38.4mmol) were dissolved in DCM (221 mL). The resulting solution was allowed to stand for 5 to 15 minutes. A compound of Formula A in which X^2 is a group of Formula (c) wherein R^7 is hydrogen and R^8 is 4-benzylsulfanylmethyl and SS is Merrifield resin (3.2g) was swelled in DCM (32 mL) and added to the thiazole-4-carboxylic acid mixture. To this reaction mixture was added DMAP (140mg; 1.15mmol), and the mixture was agitated, with frequent venting, at a temperature of about 25°C for about 10 to 24 hours. The resulting resin

was isolated and washed in succession with 1:1 DCM:THF (1x100mL), DCM (2x100mL), MeOH (2x100mL) and dioxane (3x100mL) and dried under reduced pressure to yield the corresponding compound of Formula C in which X^1 is S, R^1 is 3-benzyl-3-(2-methoxy-phenyl)-ureido and X^2 is a group of Formula (c) wherein R^7 is hydrogen and R^8 is 4-benzylsulfanylmethyl. The resin of Formula C is suspended in a minimal amount of dioxane and then treated with an 8:1:1 mixture of dioxane:TEA:Pent-2-yn-1-ol (50 mL). The resulting mixture was gently agitated for 10 to 24 hours at a temperature of 40°C. The mixture was then filtered and the residue washed with dioxane. The combined filtrate was collected and lyophilized to obtain 2-({2-[3-benzyl-3-(2-methoxy-phenyl)-ureido]-thiazole-4-carbonyl}-amino) -3-benzylsulfanyl-propionic acid pent-2-ynyl ester (standard 6).

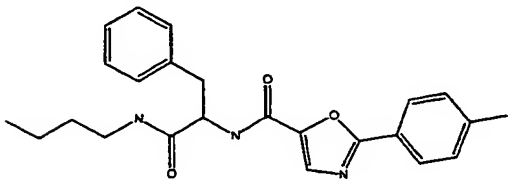
Representative Compounds of Formula II

2-(4-Hexyloxy-phenyl)-oxazole-5-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (Standard 7):

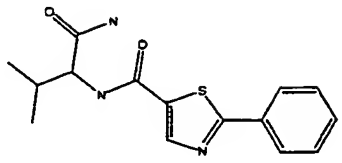
2-(4-Hexyloxy-phenyl)-oxazole-5-carboxylic acid (11.1g, 38.4mmol) and DIC (6mL; 38.4mmol) were dissolved in DCM (166 mL). The resulting solution was allowed to stand for 5 to 15 minutes. A compound of Formula D in which SS is Merrifield resin (3.2g) was swelled in DCM (32 mL) and added to the Formula B, DIC and DCM mixture. To this reaction mixture was then added DMAP (140mg; 1.15mmol), and the mixture was agitated, with frequent venting, at a temperature of about 25°C for about 10 to 24 hours. The resulting resin was isolated and washed in succession with 1:1 DCM:THF (1x100mL), DCM (2x100mL), MeOH (2x100mL) and dioxane (3x100mL) and dried under reduced pressure to yield the corresponding compound of Formula E in which R^1 is 4-hexyloxy-phenyl and X^1 is O. The compound of Formula E was suspended in a minimal amount of dioxane and then treated with 0.5M 1-benzyl-piperidin-4-ylamine in dioxane (50 mL). The resulting mixture was gently agitated for 10 to 24 hours at a temperature of 25°C. The mixture was then filtered and the filter washed with dioxane. The combined filtrate was collected and lyophilized to obtain 2-(4-hexyloxy-phenyl)-oxazole-5-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (standard 7).

Synthesis of Specific Compounds (Standards)

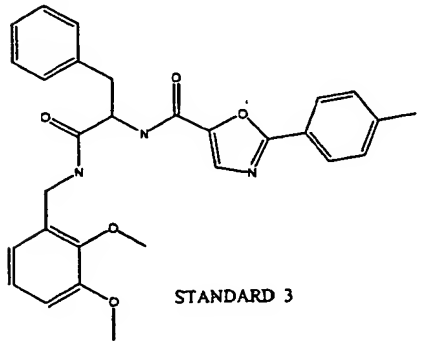
The following standard compounds of Formula I were prepared using the novel process of the present invention:



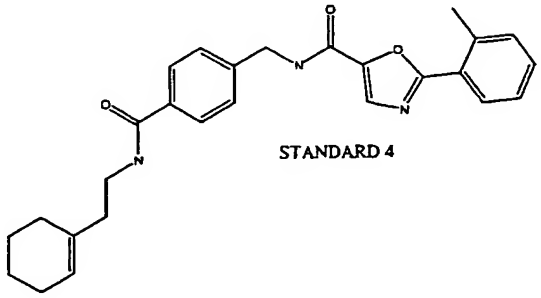
STANDARD 1



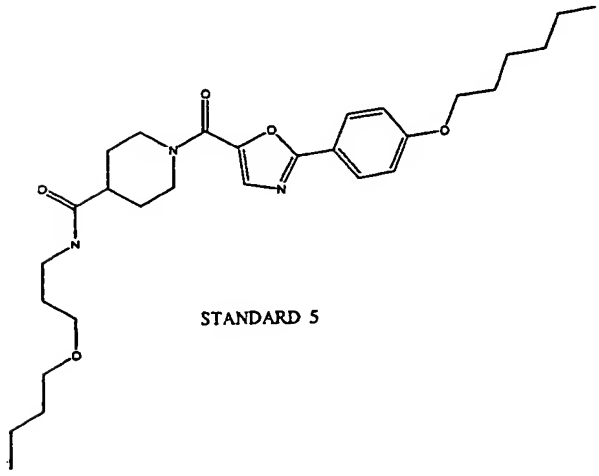
STANDARD 2



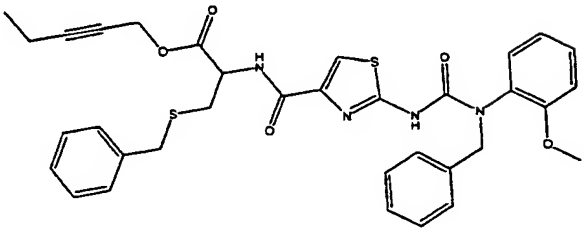
STANDARD 3



STANDARD 4



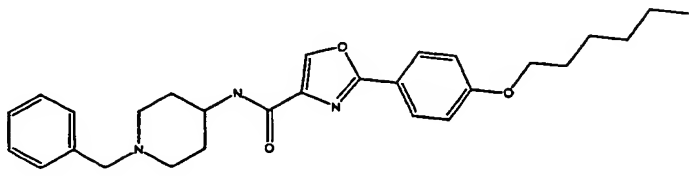
STANDARD 5



STANDARD 6

5

The following standard compound of Formula II was prepared using the novel process of the present invention:



STANDARD 7

Characterization data for the above standards are as follows:

Standard 1: Exact mass 405.2; (MH^+) m/z= 406.1

Standard 2: Exact mass 303.1; (MH^+) m/z= 303.9

Standard 3: Exact mass 499.2; (MH^+) m/z= 500.2

Standard 4: Exact mass 443.2; (MH^+) m/z= 444.1

Standard 5: Exact mass 513.3; (MH^+) m/z= 514.3

Standard 6: Exact mass 642.2; (MH^+) m/z= 643.2

Standard 7: Exact mass 461.3; (MH^+) m/z= 462.2

Analysis Procedure

A. Chromatography: All validation samples are analyzed on a Hewlett Packard HP1100 HPLC employing a Zorbax 4.6 mm x 7.5 cm SP-C18 column with a guard column. Samples are monitored at UV settings of 214 and 254 nm. The column is heated at 40°C and the flow rate is 0.800 mL per minute for all runs. Gradient elution is performed using water with 0.05% TFA (solvent A) and acetonitrile containing

0.05% TFA (solvent B) as mobile phases. Most samples are prepared as dilute solutions in acetonitrile, methanol or mixtures thereof.

HPLC Gradient:

Time (minutes)	% Solvent B
0.00	0.00
5.00	100
8.00	100.0
9.50	0.00

B. Mass Spectrometry: Identity of peaks observed by HPLC are determined by electrospray (ESI) LC/MS analysis on a Finnigan TSQ 7000 mass spectrometer with a Hewlett Packard HP1050 HPLC. Alternatively, purified compounds or relatively pure mixtures are analyzed with a Hewlett Packard 5989 particle beam mass spectrometer and Hewlett Packard 59980 LC/MS interface in either CI or EI mode, with a Hewlett Packard HP1050 HPLC using methanol as mobile phase for direct injection of samples. Most samples are prepared as dilute solutions in acetonitrile or methanol. For analysis of both the test library and production library, direct injection MS analysis is performed on the Sciex 150 MCA, Shimadzu LC-10 HPLC, according to the following conditions:

LC/MS Assay:

Mobile A:	Water (containing 0.05% AcOH and 1.0% MeOH)
Mobile B:	Methanol (containing 0.05% AcOH and 1.0% water)
Flow Rate:	0.3 mL/min
Sample volume:	10.0 μL
Column:	Zorbax 3.0 x 50.0 mm column with inline filter
Temp.:	40°C
Gradient:	0 to 100% B in 6.0 min, 100% B for 1.0 min, 0% B for 2.0 min.
Detection:	UV monitoring at 214, 254, 280, and 320 nm

DEFINITIONS

Abbreviations used: Acetonitrile (ACN); Acetic Acid (AcOH); t-butyloxycarbonyl (Boc); dichloromethane (DCM); 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ); diisopropylcarbodiimide (DIC); 4-Dimethylamino-pyridine (DMAP); electrospray ionization (ESI); Diethyl Ether (Et_2O); Ethyl acetate (EtOAc); High performance liquid chromatography (HPLC); Liquid Chromatography/Mass Spectroscopy (LC/MS); Methanol (MeOH); triethylamine (TEA); Tetrahydrofuran (THF); Trifluoroacetic Acid (TFA); tetrapyrrolidinophosphonium hexafluorophosphate (PyBOP); *N*-{(dimethylamino)(1*H*-1,2,3-triazole[4,5-*b*]pyridin-1-yl)-methylene}-*N*-methylmethan-aminium hexafluorophosphate *N*-oxide (HATU); 4-Dimethylamino-pyridine (DMAP).

"Alkyl" indicated alone means a straight or branched, saturated or unsaturated aliphatic radical having the number of carbon atoms indicated (e.g., (C_{1-6})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, etc.). Alkyl indicated as part of a larger radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when 0 atoms are indicated means a bond (e.g., (C_{0-3})alkyl of (C_{3-12})cycloalkyl(C_{0-3})alkyl means a bond, methylene, ethylene, trimethylene, 1-methylethylene, etc.).

"Alkylene" means a saturated or unsaturated, branched or unbranched, hydrocarbon divalent radical having the number of carbon atoms indicated and any ketone, thioketone, iminoketone and substituted derivative thereof (e.g., (C_{1-4})alkylene includes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), methylethylene, vinylene, ethynylene, trimethylene ($-CH_2CH_2CH_2-$), 2-oxotrimethylene ($-CH_2C(O)CH_2-$), 2-thiatrimethylene ($-CH_2C(S)CH_2-$), 2-iminotrimethylene ($-CH_2C(NH)CH_2-$), propenylene ($-CH_2CH-CH-$ or $-CH-CHCH_2-$), propanylylidene ($-CHCH_2CH_2-$),

propendiylene (-CHCH-CH-), 1-aminotetramethylene, pentamethylene, etc.). When no carbon atoms are indicated (e.g., as in (C_0)alkylene), a bond is intended.

"Alkyloxy" means the radical -OR, wherein R is alkyl as defined above, having the number of carbon atoms indicated (e.g., (C_{1-6})alkyloxy includes the radicals methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, vinyloxy, allyloxy, 1-propenyloxy, isopropenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 2-methylallyloxy, ethynyloxy, 1-propynyloxy, 2-propynyloxy, and the like).

"Array of compounds" is defined as a collection of independent (individual) compounds that are synthesized by the process of the present invention. Generally, the term 'array of compounds' indicates a collection of compounds distinct from one another. Also included in the array of compounds is a mixture of individual compounds.

Aryl means an aromatic monocyclic, polycyclic or fused polycyclic ring system containing the number of annular carbon atoms indicated, wherein each ring contained therein is comprised of 6 annular members (e.g., (C_{6-12})aryl includes phenyl, naphthalenyl, and biphenylyl).

"Burgess Reagent" is the name given to the compound $(CH_3CH_2)_3N^+S(O)_2N^-C(O)OCH_3$.

"Combinatorial Synthesis" is defined as an ordered strategy for parallel synthesis of arrays of single compounds or mixtures, by sequential addition of reagents.

"Coupling Agent" is intended to represent an additive that facilitates the course of a reaction but does not get incorporated in to the final product. Illustrative examples of coupling agents are diisopropylcarbodiimide (DIC), *N*-

hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt) and *N*-hydroxysuccinimide.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic ring, bicyclic ring assembly (directly linked by a single bond or fused) or bridged polycyclic ring assembly containing the number of annular carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-12})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclohexylyl, cyclopentylcyclohexyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthalenyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, etc.).

"Halo" means fluoro, chloro, bromo or iodo.

"Heteroaryl" means aryl, as defined herein, provided that one or more of the annular carbon atoms indicated, is replaced by heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group, and each ring contained therein is comprised of 5 to 6 annular members (e.g., hetero(C_{5-14})aryl includes thienyl, furyl, pyrrolyl, pyrimidinyl, isoxazolyl, oxaxolyl, indolyl, benzo[*b*]thienyl, isobenzofuranyl, purinyl, isoquinolyl, pterdinyl, perimidinyl, imidazolyl, 1-methylimidazolyl, 1-benzylimidazolyl, pyridyl, pyrazolyl, pyrazinyl, quinolyl, [2,4']bipyridinylyl, 2-phenylpyridyl, 4-thiazol-4-ylphenyl, 1*H*-imidazol-1-ylphenyl, and the like). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined herein, provided that one or more of the annular carbon atoms indicated is replaced by heteroatom moiety selected from -N-, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term heterocyclo(C_{5-14})alkyl includes piperidyl, pyrrolidinyl, pyrrolinyl,

imidazolidinyl, quinuclidinyl, morpholinyl, [1,4']bipiperidinylyl, 1',2'-dihydro-2*H*-[1,4']bipyridinylyl, 1-morpholin-4-ylpiperidinyl, etc.). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like.

"Heteropolycycloaryl" means polycycloaryl, as defined herein, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., heteropolycyclo(C_{8-12})aryl includes 3,4-dihydro-2*H*-quinolinyl, 5,6,7,8-tetrahydroquinolinyl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, morpholinylpyridyl, piperidinylphenyl, 1,2,3,4,5,6-hexahydro-[2,2']bipyridinylyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, and the like).

"Iminoketone derivative" means a derivative containing the moiety -C(NR)-, wherein R is hydrogen or (C_{1-6})alkyl.

"Inert solvents" as used herein represents solvents that do not react with the reagents dissolved therein. Illustrative examples of inert solvents are tetrahydrofuran (THF), methylene chloride, dichloromethane (DCM), ethyl acetate (ETOAc), dimethyl formamide (DMF), dioxane, chloroform and dimethylsulfoxide (DMSO).

"Ketone derivative" means a derivative containing the moiety -C(O)-.

"Nitro" means the radical $-NO_2$.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "any 1 to 3 annular atoms of any aromatic ring with available valences

comprising R^6 optionally independently is substituted means that the aromatic ring referred to may or may not be substituted in order to fall within the scope of the invention.

"Polycycloaryl" means a bicyclic ring assembly (directly linked by a single bond or fused) containing the number of annular carbon atoms indicated, wherein at least one, but not all, of the fused rings comprising the radical is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., polycyclo(C_{9-12})aryl includes indanyl, indenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2-dihydronaphthalenyl, cyclohexylphenyl, phenylcyclohexyl, 2,4-dioxo-1,2,3,4-tetrahydro-naphthalenyl, or the like).

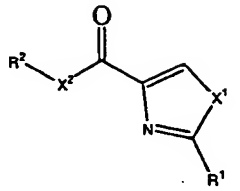
"Solid support or (SS)", as used in the present invention, signifies polymeric material for supported synthesis. A detailed description of the terms linker molecule, and solid support can be found in The Combinatorial Index, B. A. Bunin, 1998, which is incorporated herein by reference.

"Thioketone derivative" means a derivative containing the moiety -C(S)-.

WE CLAIM:

We Claim:

1. A process for synthesizing a compound or an array of compounds of Formula I:

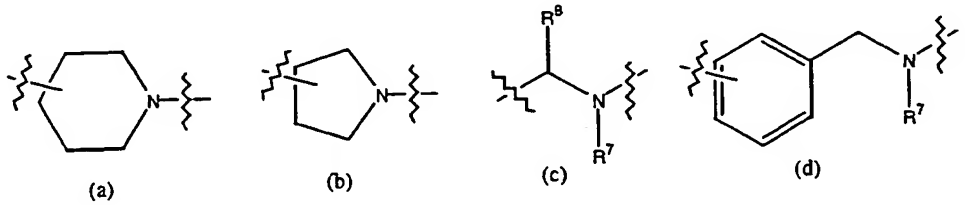


in which:

X^1 is O or S;

R^1 is $-R^3$, $-NR^3R^4$, $-NR^3C(NR^4)NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is (C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, polycyclo(C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^3NR^5R^5$, $-X^3NR^5C(O)R^5$, $-X^3NR^5C(O)OR^5$, $-X^3NR^5C(O)NR^5R^5$ and $-X^3NR^5C(NR^5)NR^5R^5$, wherein X^3 is a bond or methylene and R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl;

X^2 is a group selected from Formulae (a), (b), (c) and (d):



(a) (b) (c) (d)

R^2 is $-CH_2OH$, $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, wherein R^9, R^{10} and R^{11} independently are hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl or $-X^4R^{12}$, wherein X^4 is (C_{1-4})alkylene and R^{12} is $-OR^{13}$ or $-NR^{13}R^{14}$, wherein R^{13} and R^{14} are

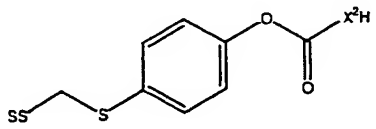
independently hydrogen, (C_{1-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl, $-X^4OR^{16}$ or $-X^4NR^{16}R^{16}$, wherein X^4 is as defined above and R^{16} at each occurrence independently is hydrogen or (C_{1-2})alkyl, wherein any aromatic moieties comprising R^9, R^{10} or R^{11} optionally independently are substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^4NR^5R^5$, $-X^4NR^5C(O)R^5$, $-X^4NR^5C(O)OR^5$, $-X^4NR^5C(O)NR^5R^5$ and $-X^4NR^5C(NR^5)NR^5R^5$, wherein X^4 and R^5 are as defined above, or R^9 and R^{10} together with the nitrogen atom to which R^9 and R^{10} are attached form hetero(C_{5-7})cycloalkyl optionally substituted with $-X^4R^{12}$, wherein X^4 and R^{12} are as defined above;

R^7 is hydrogen or (C_{1-4})alkyl; and

R^8 is (i) hydrogen, (ii) (C_{1-6})alkyl optionally substituted with $-OR^{17}$, $-SR^{17}$, $-S(O)R^{17}$, $-S(O)_2R^{17}$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{18}$, $-NR^{17}R^{18}$, $-NR^{18}C(O)R^{17}$, $-NR^{18}C(O)OR^{17}$,$-NR^{18}C(O)NR^{17}R^{18}$ or $-NR^{18}C(NR^{18})NR^{17}R^{18}$, wherein R^{17} is (C_{1-6})alkyl, (C_{1-6})alkanoylaminomethyl, (C_{3-12})cycloalkyl(C_{0-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-3})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, (C_{6-12})arylsulfonyl, hetero(C_{5-12})aryl(C_{0-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-3})alkyl and R^{18} at each occurrence independently is hydrogen or (C_{1-6})alkyl, or (iii) (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{1-3})alkyl, hetero(C_{5-12})aryl(C_{1-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{1-3})alkyl;

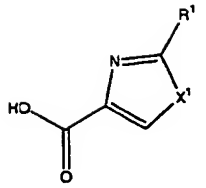
said process comprising:

(i) treating a compound of Formula A:



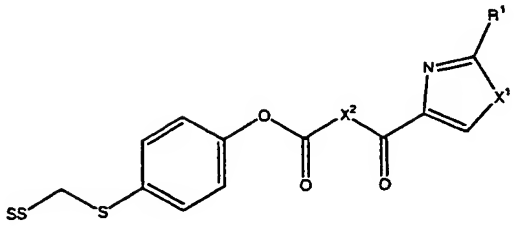
Formula A

with a compound of Formula B:



Formula B

in the presence of a coupling agent and optionally an acylation catalyst, to yield a compound of Formula C:

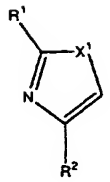


Formula C

where R^1, X^1 and X^2 are as defined above and "SS" represents a solid support; and

(ii) treating a compound or an array of compounds of Formula C with (a) a reducing agent to yield a compound or an array of compounds of Formula I where R^2 is CH_2OH, or (b) a compound of formula $R^9R^{10}NH$ or $R^{11}OH$ to yield a compound or an array of compounds of Formula I where R^2 is $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, respectively.

2. A process for synthesizing a compound or an array of compounds of Formula II:



Formula II

in which:

X^1 is O or S;

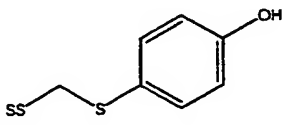
R^1 is $-R^3$, $-NR^3R^4$, $-NR^3C(NR^4)NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is (C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, polycyclo(C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^3NR^5R^5$, $-X^3NR^5C(O)R^5$, $-X^3NR^5C(O)OR^5$, $-X^3NR^5C(O)NR^5R^5$ and $-X^3NR^5C(NR^5)NR^5R^5$, wherein X^3 is a bond or methylene and R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl;

R^2 is $-CH_2OH$, $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, wherein R^9, R^{10} and R^{11} independently are hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl or $-X^4R^{12}$, wherein X^4 is (C_{1-4})alkylene and R^{12} is $-OR^{13}$ or $-NR^{13}R^{14}$, wherein R^{13} and R^{14} are independently hydrogen, (C_{1-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl, $-X^4OR^{16}$ or $-X^4NR^{16}R^{16}$, wherein X^4 is (C_{1-4})alkylene and R^{16} at each occurrence independently is hydrogen or (C_{1-2})alkyl, wherein any aromatic moieties comprising R^9, R^{10} or R^{11} optionally independently are substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^4NR^5R^5$, $-X^4NR^5C(O)R^5$, $-X^4NR^5C(O)OR^5$, $-X^4NR^5C(O)NR^5R^5$ and $-X^4NR^5C(NR^5)NR^5R^5$, wherein X^4 and R^5 are as defined above, or R^9 and R^{10} together

with the nitrogen atom to which R^9 and R^{10} are attached form hetero(C_{5-7})cycloalkyl optionally substituted with $-X^4R^{12}$, wherein X^4 and R^{12} are as defined above;

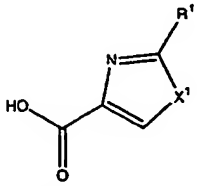
said process comprising:

(1) treating a compound of Formula D:



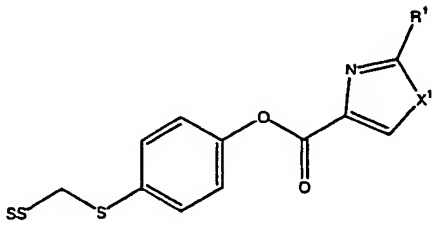
Formula D

with a compound of Formula B:



Formula B

in the presence of a coupling agent and optionally an acylation catalyst, to yield a compound of Formula E:



Formula E

where R^1 and X^1 are as defined above and "•" represents a solid support; and

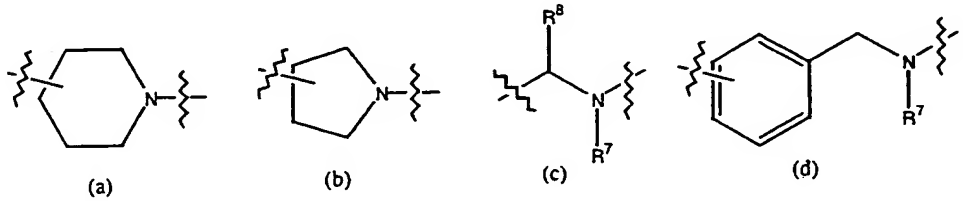
(2) treating a compound or an array of compounds of Formula E with (a) a reducing agent to yield a compound or an array of compounds of Formula II, where R^2 is CH_2OH, or (b) a compound of formula $R^9R^{10}NH$ or $R^{11}OH$ to yield a compound or an array of compounds of Formula II where R^2 is $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, respectively.

3. The process of claim 1 in which:

X^1 is O or S;

R^1 is $-R^3$, $-NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is (C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl or $-OR^5$ wherein R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl;

X^2 is a group selected from Formulae (a), (b), (c) and (d):



R^2 is $-CH_2OH$, $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, wherein R^9, R^{10} and R^{11} independently are hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl or $-X^4R^{12}$, wherein X^4 is (C_{1-4})alkylene and R^{12} is $-OR^{13}$ or $-NR^{13}R^{14}$, wherein R^{13} and R^{14} are independently hydrogen, (C_{1-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl, $-X^4OR^{16}$ or $-X^4NR^{16}R^{16}$, wherein X^4 is as defined above and R^{16} at each occurrence independently is hydrogen or (C_{1-2})alkyl, wherein any aromatic moiety comprising R^9, R^{10} or R^{11} optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl,

halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^4NR^5R^5$, $-X^4NR^5C(O)R^5$, $-X^4NR^5C(O)OR^5$, $-X^4NR^5C(O)NR^5R^5$ and $-X^4NR^5C(NR^5)NR^5R^5$, wherein X^4 and R^5 are as defined above, or R^9 and R^{10} together with the nitrogen atom to which R^9 and R^{10} are attached form hetero(C_{5-7})cycloalkyl optionally substituted with $-X^4R^{12}$, wherein X^4 and R^{12} are as defined above;

R^7 is hydrogen or (C_{1-4})alkyl; and

R^8 is (i) hydrogen, (ii) (C_{1-6})alkyl optionally substituted with $-OR^{17}$, $-SR^{17}$, $-S(O)R^{17}$, $-S(O)_2R^{17}$, $-NR^{18}C(O)OR^{17}$, or $-NR^{18}C(NR^{18})NR^{17}R^{18}$, wherein R^{17} is (C_{1-6})alkyl, (C_{1-6})alkanoylaminomethyl or (C_{3-12})cycloalkyl(C_{0-3})alkyl and R^{18} at each occurrence independently is hydrogen or (C_{1-6})alkyl.

4. The process of claim 2 wherein:

X^1 is O or S;

R^1 is $-R^3$, $-NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is (C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl or $-OR^5$ wherein R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl;

R^2 is $-CH_2OH$, $-C(O)NR^9R^{10}$ or $-C(O)OR^{11}$, wherein R^9, R^{10} and R^{11} independently are hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl or $-X^4R^{12}$, wherein X^4 is (C_{1-4})alkylene and R^{12} is $-OR^{13}$ or $-NR^{13}R^{14}$, wherein R^{13} and R^{14} are independently hydrogen, (C_{1-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, polycyclo(C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, heteropolycyclo(C_{6-12})aryl(C_{0-6})alkyl, $-X^4OR^{16}$ or $-X^4NR^{16}R^{16}$, wherein X^4 is as described above and R^{16} at each occurrence independently is hydrogen or (C_{1-2})alkyl, wherein any aromatic moiety comprising R^9, R^{10} or R^{11} optionally is substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, -

$X^4NR^5R^5$, $-X^4NR^5C(O)R^5$, $-X^4NR^5C(O)OR^5$, $-X^4NR^5C(O)NR^5R^5$ and $-X^4NR^5C(NR^5)NR^5R^5$, wherein X^4 and R^5 are as defined above, or R^9 and R^{10} together with the nitrogen atom to which R^9 and R^{10} are attached form hetero(C_{5-7})cycloalkyl optionally substituted with $-X^4R^{12}$, wherein X^4 and R^{12} are as defined above.

5. The process of claim 3 wherein step (i) comprises treating a compound of Formula A with a compound of Formula B in the presence of a coupling agent selected from DIC, PyBOP, and HATU, and a catalyst selected from DMAP and 4-pyrrolidinopyridine.

6. The process of claim 5 wherein step (i) is carried out in the presence of an inert solvent selected from DCM, THF, and chloroform at a temperature ranging from about 15°C to about 35°C.

7. The process of claim 6 wherein the reducing agent in step (i)(a) is $LiBH_4$.

8. The process of claim 7 wherein the inert solvent in step (ii) is selected from THF, methylene chloride, DCM, ethyl acetate, DMF, dioxane, chloroform and DMSO, and step (ii)(a) is carried out at a temperature ranging from about -30°C to about 35°C.

9. The process of claim 8 wherein step (ii)(b) is carried out at a temperature ranging from about 10°C to about 50°C.

10. An array of compounds synthesized by the process of Claim 1.

11. The process of claim 4 wherein step (1) comprises treating a compound of Formula D with a compound of Formula B in the presence of a coupling agent selected from DIC, PyBOP, and HATU, and a catalyst selected from DMAP and 4-pyrrolidinopyridine.

12. The process of claim 11 wherein step (1) is carried out in the presence of an inert solvent selected from DCM, THF and chloroform, and at a temperature ranging from about 15°C to about 35°C.

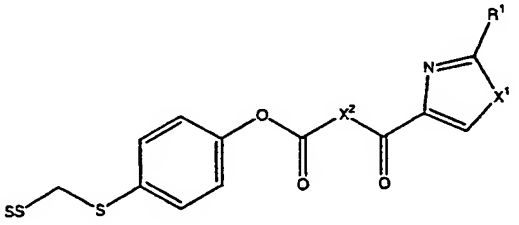
13. The process of claim 12 wherein the reducing agent in step (2)(a) is $LiBH_4$.

14. The process of claim 13 wherein the inert solvent in step (2) is selected from THF, methylene chloride, DCM, ethyl acetate, DMF, dioxane, chloroform and DMSO, and step (2)(a) is carried out at a temperature ranging from about -30°C to about 35°C.

15. The process of claim 14 wherein step (2)(b) is carried out at a temperature ranging from about 10°C to about 50°C.

16. An array of compounds synthesized by the process of claim 2.

17. A process for synthesizing a compound or an array of compounds of Formula C:



Formula C

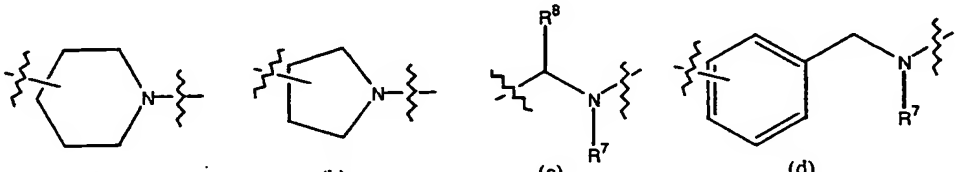
in which:

X^1 is O or S;

R^1 is $-R^3$, $-NR^3R^4$, $-NR^3C(NR^4)NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is (C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, polycyclo(C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3

substituents selected independently from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^3NR^5R^5$, $-X^3NR^5C(O)R^5$, $-X^3NR^5C(O)OR^5$, $-X^3NR^5C(O)NR^5R^5$ and $-X^3NR^5C(NR^5)NR^5R^5$, wherein X^3 is a bond or methylene and R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl;

X^2 is a group selected from Formulae (a), (b), (c) and (d):

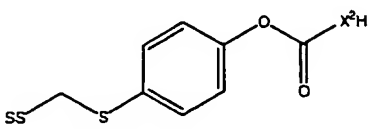


R^7 is hydrogen or (C_{1-4})alkyl; and

R^8 is (i) hydrogen, (ii) (C_{1-6})alkyl optionally substituted with $-OR^{17}$, $-SR^{17}$, $-S(O)R^{17}$, $-S(O)_2R^{17}$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{18}$, $-NR^{17}R^{18}$, $-NR^{18}C(O)R^{17}$, $-NR^{18}C(O)OR^{17}$, $-NR^{18}C(O)NR^{17}R^{18}$ or $-NR^{18}C(NR^{18})NR^{17}R^{18}$, wherein R^{17} is (C_{1-6})alkyl, (C_{1-6})alkanoylaminomethyl, (C_{3-12})cycloalkyl(C_{0-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-3})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, (C_{6-12})arylsulfonyl, hetero(C_{5-12})aryl(C_{0-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-3})alkyl and R^{18} at each occurrence independently is hydrogen or (C_{1-6})alkyl, or (iii) (C_{3-12})cycloalkyl(C_{1-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-3})alkyl, (C_{6-12})aryl(C_{1-3})alkyl, hetero(C_{5-12})aryl(C_{1-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{1-3})alkyl;

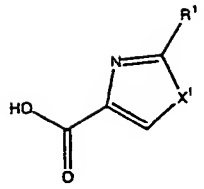
said process comprising:

(i) treating a compound of Formula A:



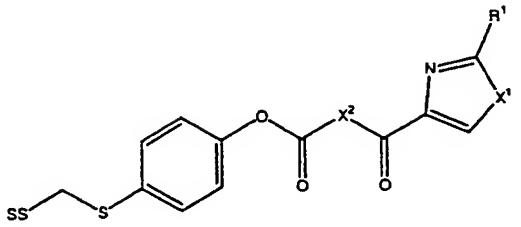
Formula A

with a compound of Formula B:



Formula B

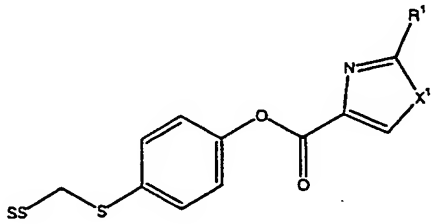
in the presence of a coupling agent and optionally an acylation catalyst, to yield a compound of Formula C:



Formula C

where R^1, X^1 and X^2 are as defined above and "SS" represents a solid support.

18. A process for synthesizing a compound or an array of compounds of Formula E:



Formula E

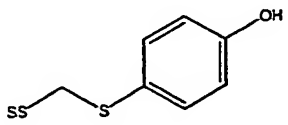
in which:

X^1 is O or S;

R^1 is $-R^3$, $-NR^3R^4$, $-NR^3C(NR^4)NR^3R^4$ or $-NR^3C(O)NR^3R^4$ wherein R^3 is (C_{1-10})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, polycyclo(C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl$(C_{0-}$

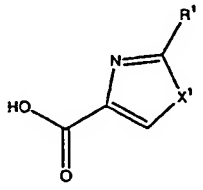
$_3$)alkyl or heteropolycyclo(C_{6-12})aryl(C_{0-3})alkyl and R^4 is hydrogen or (C_{1-6})alkyl, wherein any aromatic moiety comprising R^1 optionally is substituted with 1 to 3 substituents selected independently from halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^5$, $-C(O)R^5$, $-C(O)OR^5$, $-C(O)NR^5R^5$, $-S(O)_2NR^5R^5$, $-X^3NR^5R^5$, $-X^3NR^5C(O)R^5$, $-X^3NR^5C(O)OR^5$, $-X^3NR^5C(O)NR^5R^5$ and $-X^3NR^5C(NR^5)NR^5R^5$, wherein X^3 is a bond or methylene and R^5 at each occurrence independently is hydrogen or (C_{1-6})alkyl;

said process comprising treating a compound of Formula D:



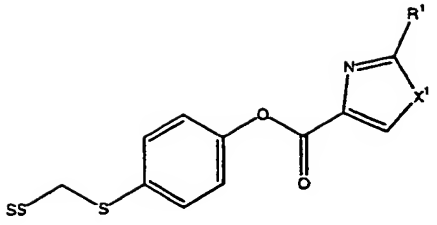
Formula D

with at least a compound of Formula B:



Formula B

in the presence of a coupling agent and optionally an acylation catalyst, to yield a compound of Formula E:



Formula E

where R^1 and X^1 are as defined above and "SS" represents a solid support.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 00/21051

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B61/00 C07D263/34 C07D263/32 C07D277/56 C07D277/20
C07D413/12 C07D417/12 C07K5/078

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 04257 A (UNIVERSITY OF PITTSBURGH) 5 February 1998 (1998-02-05) the whole document	10,16
X	WIPF P ET AL: "Combinatorial synthesis and biological evaluation of library of small-molecule Ser/Thr-protein phosphatase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 5, no. 1, 1997, pages 165-177, XP002119507 ISSN: 0968-0896 the whole document	10,16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 November 2000	28/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 00/21051

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	FANTAUZZI P P ET AL: "Synthesis of Diverse Tetrahydro -beta-Carboline-3-Carboxamides and -2,3-Bis-lactams On a Versatile 4-Hydroxythiophenol-Linked Solid Support" TETRAHEDRON LETTERS, vol. 39, no. 11, 12 March 1998 (1998-03-12), pages 1291-1294, XP004107917 ISSN: 0040-4039 the whole document	1-18
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Y	HALL G E ET AL: "Chemistry of Micrococcin P. Part VIII. A method for the degradation of thiazol-4-carboxylic acids" JOURNAL OF THE CHEMICAL SOCIETY (C), no. 16, 1966, pages 1357-1360, XP002151533 the whole document, particularly page 1358, left-hand column, 6th paragraph	1-18
P,Y	WO 00 03681 A (EXYS PHARMACEUTICALS, INC.) 27 January 2000 (2000-01-27) the whole document	1-18
A	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002151534 Beilstein Registry Number 804286 and 793856 & J. CHEM. SOC., 1961, pages 405-411,	10

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Inte. ional Application No
PCT/US 00/21051

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002151535 Beilstein Registry Number 5676684 & J.ORG. CHEM., vol. 51, no. 24, 1986, pages 4580-4585,	10
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A	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002151537 Beilstein Registry Number 791970 & J. GEN. CHEM. USSR, vol. 33, 1963, pages 3590-3592,	16
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intl. Jonal Application No
PCT/US 00/21051

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		EP 0959884 A	01-12-1999
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		US 5856506 A	05-01-1999
		US 6040323 A	21-03-2000
WO 0003681 A	27-01-2000	AU 4997199 A	07-02-2000